MATHEMATICAL MODELING OF THE SPREAD OF HANTAVIRUS INFECTION

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MATHEMATICAL MODELING OF THE SPREAD OF HANTAVIRUS INFECTION

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LIST OF ABBREVIATIONS

AK	Abramson and Kenkre
EN	Epidemic Nephritis
FTCS	Forward Time Central Space Scheme
HCPS	Hantavirus Cardiopulmonary Syndrome
HFRS	Hemorrhagic Fever with Renal Syndrome
HPS	Hantavirus Pulmonary Syndrome
ODE	Ordinary Differential Equation
ODEs	Ordinary Differential Equations
PDE	Partial Differential Equation
PDEs	Partial Differential Equations
SI	Susceptible-Infected
SIS	Susceptible-Infected-Susceptible

PEMODELAN MATEMATIK PENYEBARAN

JANGKITAN HANTAVIRUS

ABSTRAK

Hantavirus adalah ejen jangkitan penyakit yang boleh menyebabkan kematian di kalangan manusia. Hantavirus berperumahkan tikus tanpa memberi kesan kepada perumah itu sendiri. Banyak usaha telah dilakukan oleh para penyelidik untuk membangun dan menganalisa model matematik jangkitan hantavirus. Suatu model matematik mudah yang menjelaskan pembiakan jangkitan hantavirus ke atas tikus telah dicadang dan dibangunkan oleh Abramson dan Kenkre (2002) yang mana model tersebut mengambilkira ciri ruang dan masa bagi jangkitan ini. Model matematik Abramson dan Kenkre (2002) boleh dimurnikan dan dibangunkan selanjutnya dengan mengambil kira pelbagai faktor. Ini kemudiannya akan membolehkan kita untuk menganalisis senario yang lebih realistik dan membantu untuk lebih memahami jangkitan hantavirus. Dalam tesis ini, kami melanjutkan model Abramson dan Kenkre (2002) untuk mendapatkan model baru bagi menerangkan pelbagai kesan. Kami membangunkan, menganalisis dan menyiasat model baru matematik berangka (melibatkan sistem persamaan pembezaan biasa (ODE) dan persamaan pembezaan separa (PDE) untuk mendalami kesan daripada penuaian populasi, biodiversiti, penghantaran dinamik dan tindak balas penyebaran. Penulis turut menyiasat kesan peringkat tinggi tidak linear ke atas jangkitan "refugia" bagi takungan penyakit berjangkit. Keputusan yang diperolehi oleh model Abramson dan Kenkre bagi ruang lanjutan menunjukkan bagaimana faktor persekitaran boleh membawa kepada kepupusan jangkitan di kawasan setempat dan kegigihan dalam

kawasan setempat yang lain, di bawah syarat persekitaran yang bersesuaian, jangkitan akan berkembang. Kami turut meluaskan Abramson dan Kenkre model dengan memasukkan proses penuaian dan mengkaji kesan strategi penuaian yang berbeza ke atas pembiakan jangkitan hantavirus ke atas tikus. Kami turut mengubahsuai model biodiversiti Peixoto and Abramson (2006) untuk memasukkan kesan “alien” atau pemangsa dan mengkaji ramalan model. Apabila populasi tikus dan “alien” atau pemangsa dalam persaingan, populasi “alien” atau pemangsa memberi kesan pengurangan kekerapan jangkitan tikus. Penuaian populasi dan “alien”/pemangsa boleh digunakan untuk mengawal dan mengurangkan bilangan spesis yang bersaing untuk menstabilkan populasi pada keseimbangan yang berterusan. Hantavirus dihantar kepada manusia melalui gigitan dan calaran tikus yang dijangkiti. Berdasarkan kajian Li et al. (2009), kami membangunkan model baru matematik untuk penghantaran dinamik hantavirus dalam manusia sebagai perumah dan tikus sebagai vektor. Kami mendapatkan nombor asas pembiakan, R_0 dan menunjukkan bahawa peningkatan kekerapan gigitan dan cakaran apabila populasi tikus yang dijangkiti yang terlalu tinggi akan menyebabkan risiko peningkatan penyebaran jangkitan hantavirus kepada populasi manusia. Kami turut menggunakan teknik eksperimen berangka untuk mengkaji kesan mekanisme resapan, terutamanya pemalar resapan, D, ke atas fenomena kepupusan dan kegigihan tikus dan "alien" (sebagai pemangsa) untuk penyebaran jangkitan hantavirus dalam ruang satu dimensi. Dengan menganalisis ciri-ciri persamaan yang sesuai, kestabilan tempatan bagi keseimbangan dikaji yang melibatkan sistem ODE dan PDE. Dengan teorem kestabilan Liapunov, kami memperolehi syarat untuk asimptot kestabilan global kawasan "interior", "trivial", bebas penyakit dan keseimbangan yang endemik bagi sistem ODE. Penyelesaian model-model

matematik telah memberikan lebih kefahaman tentang faktor yang mempengaruhi jangkitan hantavirus dan faktor-faktor tersebut diterangkan dengan lebih terperinci dalam tesis ini. Model-model yang telah dibangunkan, dianalisis dan disiasat secara berangka dalam tesis ini yang boleh menjadi asas untuk penyelidikan selanjutnya.

MATHEMATICAL MODELING OF THE SPREAD

OF HANTAVIRUS INFECTION

ABSTRACT

Hantaviruses are infectious agents that can cause diseases resulting in deaths of humans. Hantavirus are hosted by rodents without affecting the hosts themselves. Many efforts have been carried out by researchers to develop and analyze mathematical models of hantavirus infection. A simple mathematical model describing the spread of the hantavirus infection in rodents has been proposed and developed by Abramson and Kenkre (2002) wherein the model takes into account the temporal and spatial characteristics of this infection. The mathematical model of Abramson and Kenkre (2002) can be refined and developed further to take into account various other factors. This would then enable us to analyse more realistic scenarios and assist in the greater understanding of hantavirus infection. In this thesis we extend the model of Abramson and Kenkre (2002) so as to obtain new models describing various effects. We develop, analyse and investigate numerically new mathematical models (involving systems of ordinary differential equation (ODE) and partial differential equation (PDE)) to factor in the effects of population harvesting, biodiversity, transmission dynamic and reaction-diffusion. We also investigate the effects of high-order nonlinearities on the shapes of infection refugia of the reservoir of an infectious disease. The results obtained by Abramson and Kenkre spatially extended model show how environmental factors could lead to the extinction of the infection in localized areas and its persistence in other localized areas from which, under favorable environmental conditions it can spread again. We extend Abramson

and Kenkre model to include the process of harvesting and study the impact of different harvesting strategies in the spread of the hantavirus infection in rodents. We also modify the Peixoto and Abramson (2006) biodiversity model to include the effect of aliens or predators and study the predictions of the modified model. When rodent and alien or predator populations are in competition, the alien or predator populations have the effect of reducing the prevalence of infection. Population harvesting and aliens/predators may be used for control and reduce the number of competing species to stabilize the populations at a persistent equilibrium. Hantavirus is transmitted to humans through rodent bites and scratches of infected rodents. Based on Li et al. (2009), we develop a new mathematical model for the transmission dynamics of hantavirus in the human as host and the rodent as vector. We obtain the basic reproductive number, R_0 and show that an increasing frequency of bites and scratches when the population of infected rodent is too high will cause increasing risk of spread of the infection to human population. We also employed the numerical experiments technique in order to study the effect of diffusion mechanism, particularly the diffusion constant *D*, on the extinction and persistence phenomena of rodent and alien (as predator) for the spread of the hantavirus infection in one-space dimension. By analysing the corresponding characteristic equations, the local stability of the equilibriums are investigated involving systems of ODE and PDE. By the Liapunov stability theorem, we obtain the condition for the global asymptotical stability of the interior, trivial, disease-free and the endemic equilibriums for the systems of ODE. The solution of the mathematical models has enabled greater understanding of the various factors that influence hantavirus infection and they are described in greater detail in this thesis. The models that have

been developed, analysed and investigated numerically in this thesis can be the basis for further research.

CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Hantaviruses are carried by rodents and can be transmitted via aerosolized excreta to humans beings, causing hemorrhagic fever with renal syndrome (HFRS) or hantavirus pulmonary syndrome (HPS). Over 300 viruses belong to the hantavirus class of viruses family but only a few species are harmful to humans. Hantaviruses are carried by different rodent species; principally each virus genotype has a specific rodent host. Hantavirus infection in a rodent host usually is asymptomatic and persistent (Kaukinen, 2004). Asymptomatic hantavirus infection is defined as laboratory evidence of acute hantavirus infection (presence of hantavirus-specific immunoglobulin M (IgM) antibodies) in persons with no documented concurrent illness (Toro et al., 1998).

Mathematical modeling of the spread of epidemics is important and offers useful insights and possibly predictive capabilities. The hantavirus infection is carried by rodents that move from location to location, and is transmitted to other rodents through what are probably aggressive encounters (fights). The rodents do not die nor are otherwise impaired from the contraction of the virus. There is no “vertical transmission” of the disease, i.e., there are no rodents born infected. Humans infected

by the rodents virus have no feedback effects on the rodents in the infection process (Kenkre et al., 2007).

Abramson and Kenkre (2002) stated that the *Sin Nombre* virus (a type of hantavirus) was the infectious agent that caused an outbreak of hantavirus pulmonary syndrome in the North American Southwest in 1993. Each hantavirus is hosted by a single rodent species which become infected. The rodent does not lose its infection and infects human that come into contact with it or its excreta. A mathematical model was introduced by Abramson and Kenkre (2002) which incorporates decay by death of the rodent population, the increase by birth the effect of the environment to stabilize the population and rodent movement by diffusion. Two characteristics of hantavirus infection have been observed in the field can be replicated from the simulation results of the mathematical model developed by Abramson and Kenkre (2002). One is that the infection can completely disappear from the rodent population if environmental conditions are inadequate and only to reappear when environmental conditions change. There is also a spatial characteristic in that there are indications of focality of the infection. These "refugia" of the rodent population can expand or contract, carrying the infection to other places (Abramson and Kenkre, 2002). There are certain aspects of the mathematical model of Abramson and Kenkre (2002), in particular relating to the refugia, which can be investigated further.

Population harvesting is defined as the removal of a constant number of individual from a population during each time period (Miner and Wicklin, 1996). Such a policy has been used to stabilise population in the environment with limited resources or environmental parameter. Hantavirus can cause diseases which have

been proven to be fatal in humans. It would seem somewhat natural to investigate the effect of population harvesting on the spread of hantavirus infection.

Biodiversity or biological diversity can be considered of three levels: genetic diversity, species diversity and ecosystem diversity. Solomon et al. (2005) states that biodiversity is decreasing worldwide. In real-life, rodents not only share resources among themselves, but they also share with other species (so called “alien” species). The competition between rodents and “alien” species should be taken into account. Some research that have been conducted indicate that biodiversity play an important role to control the spread of hantavirus (Mills, 2006; Peixoto and Abramson, 2006). In this thesis, we will investigate the effect of biodiversity on the spread of hantavirus infection and propose a suitable mathematical model based on the Peixoto and Abramson (2006) model.

The transmission of hantavirus infection is clearly important. But not much effort had been done by researchers to study the transmission of hantavirus infection. The transmission of hantavirus to humans occur mainly through rodent bites and scratches of infected rodent. Therefore, we propose a mathematical model for the transmission of infection of hantavirus with the human as host and the rodent as vector. In addition, we will investigate the effect of human population on the spread of hantavirus infection.

The problem of spatial effects is an important problem in ecology which can lead the emergence of several types of spatial phenomena. Reaction-diffusion systems can be utilized to elucidate such phenomena for the effects of habitat

geometry and heterogeneity of environment on the extinction, persistence and coexistence of animal species. Many efforts had been done by researchers to study this phenomenon. Related studies on this phenomenon can be found in Mohd and Abu Hasan (2012), Cantrell and Cosner (2003), Seno (1988) and Van Kirk and Lewis (1997). According to Tatum (2010), reaction-diffusion model is a system of mathematical equations that describe how the concentrations of one or more substances are affected by reaction and diffusion processes. We will also focus our study on the effect of reaction-diffusion on a biodiversity of hantavirus infection. In particular, we will consider how the spatial effect of diffusion can influence rodents and alien (as predator) species in a finite habitat.

There are clearly several aspects of hantavirus infection which deserve further investigation. A detailed discussion of the issues will be carried out in the relevant chapters which follow.

1.2 OBJECTIVE

As mentioned, Abramson and Kenkre (2002) introduced a mathematical model for hantavirus infection and Peixoto and Abramson (2006) were the first to discuss the effects of biodiversity.

The objectives of this thesis is to

- analyse model of the spread of hantavirus infection which models the effect of population hantavirus infection. Numerical experiments will be conducted on the basic model of Abramson and Kenkre (2002) to bring out the salient points of the basic model and to verify the

theoretical conclusions of Abramson and Kenkre (2002) and to provide the backdrop for this thesis.

- highlight virus relation to refugia to the model of Abramson and Kenkre (2002) and also analyse the spatial extension model of hantavirus infection. Numerical experiments will be conducted on the spatial extension of the Abramson and Kenkre (2002) model to bring out the salient points of the model and to verify the theoretical conclusion.
- develop and analyse the new mathematical model which includes the effect of population harvesting and study the predictions of the model. Numerical experiments will be conducted on a new mathematical model which extends the work of Abramson and Kenkre's (2002) model.
- develop and analyse a model which assumes the aliens in the model not only compete with rodents but are predators of rodents. Numerical experiments will be conducted on the biodiversity model of Peixoto and Abramson (2006) to highlight certain features of the model.
- develop and analyse a mathematical model for the transmission dynamic of hantavirus infection. Numerical experiments will be conducted on the transmission dynamic model.
- develop and analyse a mathematical model for the reaction-diffusion on a biodiversity of hantavirus infection. Numerical experiments will be conducted on the reaction-diffusion model to illustrate the analytical results observed.

1.3 METHODOLOGY

This thesis develops mathematical models based on systems of differential equation. These mathematical models build on the model for hantavirus infection developed by Abramson and Kenkre (2002). Then, the models are analysed using standard qualitative approaches. The systems of differential equations are solved using numerical methods and numerical experiments are conducted to study the behaviour of the mathematical models.

In the next section, we will discuss the selected numerical simulation technique, namely Runge-Kutta method and Forward Time Central Space (FTCS) Scheme. The details of each method are given as follows:

1.3.1 RUNGE-KUTTA METHOD

The Matlab function `ode45` was used in all of our numerical experiments. `ode45` is based on an explicit Runge-Kutta (4,5) formula, the Dormand-Prince pair and it is a one-step solver. ode45 is faster and more accurate but it uses large step sizes that can produce a solution plot (Palm, 1999). Computer simulations will be used for various parameter values. The Runge-Kutta method is discussed as exhibited below.

The Runge-Kutta method is an iterative methods for the solutions of ODEs. The Runge-Kutta-Fehlberg (RKF45) developed by Fehlberg (1969), based on the class of Runge-Kutta methods is a way to resolve the mathematical modeling

problem. It has a procedure to determine if the proper step *h* is being used. At each step, two different approximations for the solution are made and compared. If the two answers are in close agreement, the approximation is accepted. If the two answers do not agree to a specified accuracy, the step size is reduced. If the answers agree to more significant digits than required, the step size is increased. The Runge-Kutta-Fehlberg algorithm uses both a fifth and a fourth-order Runge-Kutta methods. The error of the Runge-Kutta-Fehlberg algorithm is estimated by subtracting these two values and can be used for adaptive step sizing. The updated formula for the fifth-fourth order Runge-Kutta-Fehlberg algorithm is shown below (Mathews and Fink, 2004).

$$
\begin{aligned}
k_1 &= f(t_i, y_i)h, \\
k_2 &= f\left(t_i + \frac{1}{4}h, y_i + \frac{1}{4}k_1\right)h, \\
k_3 &= f\left(t_i + \frac{3}{8}h, y_i + \frac{3}{32}k_1 + \frac{9}{32}k_2\right)h, \\
k_4 &= f\left(t_i + \frac{12}{13}h, y_i + \frac{1932}{2197}k_1 - \frac{7200}{2197}k_2 + \frac{7296}{2197}k_3\right)h, \\
k_5 &= f\left(t_i + \frac{1}{13}h, y_i + \frac{439}{216}k_1 - 8k_2 + \frac{3860}{513}k_3 - \frac{845}{4104}k_4\right)h, \\
k_6 &= f\left(t_i + \frac{1}{2}h, y_i - \frac{8}{27}k_1 + 2k_2 - \frac{3544}{2565}k_3 + \frac{1859}{4104}k_4 - \frac{11}{4104}k_5\right)h, \\
y_{i+1} &= y_i + \left(\frac{25}{216}k_1 + \frac{1408}{2565}k_3 + \frac{2197}{4104}k_4 - \frac{1}{5}k_4\right), \\
z_{i+1} &= z_i + \left(\frac{16}{135}k_1 + \frac{6656}{1825}k_3 + \frac{28561}{56430}k_4 - \frac{9}{50}k_5 + \frac{2}{55}k_6\right),
\end{aligned}
$$

where *y* is a fourth-order Runge-Kutta and *z* is a fifth-order Runge-Kutta. An estimate of the error can be obtained by subtracting the two values obtained. If the error exceeds a specified threshold, the results can be recalculated using a smaller

step size. The approach to estimating the new step size is shown below.

$$h_{\text{new}} = h_{\text{old}}\left(\frac{\varepsilon_{\text{ET}} h_{\text{old}}}{2\left|z_{i+1} - y_{i+1}\right|}\right)^{\frac{1}{4}}$$

where ε_{ET} is the error tolerance.

In addition, the fourth-order Runge-Kutta method has the error per step on the order of h^5 while the total accumulated error has an order of h^4 (Christodoulou, 2009). Goh et al. (2009) stated that the fourth-order Runge-Kutta method provides solutions in discretized form, only at two ends of the time interval. It is a good choice because it is quite accurate, stable and easy to program. Meanwhile, the fifth-order Runge-Kutta method has the error per step on the order of h^6 while the total accumulated error has an order of h^4 (Christodoulou, 2009). The Runge-Kutta-Fehlberg has the error per step on the order of h^4 while the total accumulated error has order of h^5 (Filiz, 2014). Therefore, the Runge-Kutta-Fehlberg method has a smaller error compared to the other order of Runge-Kutta method.

We simulate the solutions of all of our numerical experiments using this method in Chapter 3, 5, 6 and 7.

1.3.2 FORWARD TIME CENTRAL SPACE (FTCS) SCHEME

We will solve the spatial extension of the Abramson and Kenkre (2002) model by using the Forward Time Central Space (FTCS) Scheme finite-difference method. The finite-difference method is a numerical method based on subdividing the domain of the problem by introducing a mesh of discrete points for each of the independent variables. Computer simulations using Matlab will be used for various parameter values. In the following discussion a basic approach will be taken to introduce the FTCS scheme.

In this section, we introduced the Forward Time Central Space (FTCS) scheme. The FTCS scheme is an explicit method. The basic idea to solve the spatial extension partial differential equation using FTCS scheme is to approximate the differential equations by a system of algebraic equations. It is a first order accurate in time $\left(O(h)\text{accurate}\right)$ and second order accurate in space $\left(O\left(h^2\right)\text{accurate}\right)$. This scheme is simple to code and easy to use because it does not require solution of a system of simultaneous equation, but this scheme is not unconditionally stable, meaning that if one choose too large a time step $\Delta t,$ the scheme will produce chaotic and meaningless solution. For FTCS scheme to be stable, the time step Δt must be chosen such that $\Delta t \le \frac{1}{2}(\Delta x)^2$ where Δx is a step size. The FTCS scheme is consistent with the original equation since the truncation error vanishes in the limit of small Δx and Δt.

Another important fact to note is that the FTCS scheme is obtained based on subdividing the domain problem. This is done by introducing a mesh of discrete points for each of the independent variables.

In Chapters 4 and 8, the numerical experiments study of spatial extension model developed by Abramson and Kenkre (2002) and the reaction-diffusion model is conducted via this method.

The results of numerical experiments are displayed in graphical and tabular form so as to enable us to make conclusions.

1.4 THESIS OUTLINE

In chapter two, we study and discuss the literature related to the basic model of Abramson and Kenkre (2002), spatial extension model developed by Abramson and Kenkre (2002) as well Kumar et al. (2010), the background of biodiversity models, the Peixoto and Abramson model, one rodent, one alien (as predator) model and their parameters, the vector-host model developed by Li et al. (2011) to quantify spread of disease by estimating average number of secondary infections in wholly susceptible population. Finally, we will study and discuss research related to the Lotka-Volterra predator-prey model conducted by Mohd and Abu Hasan (2012) and their parameters. The discussion of the six objectives considered are presented in section 2.2 through section 2.7, respectively.

In chapter three, we study the basic mathematical model of Abramson and Kenkre for hantavirus infection and we will carry out some simulations to highlight certain features of the model. By the term "basic mathematical model" (as opposed to mathematical model) we mean that we are ignoring spatial extension in the mathematical model of Abramson and Kenkre (2002).

We will then discuss some aspects of the spatial extension of the basic model. To facilitate this, we will need to consider the (full) mathematical model of Abramson and Kenkre (2002). The basic mathematical model is a system of ordinary differential equations (ODEs) with the dependent variable being the susceptible rodent r_s, infected rodent r_i and the independent variable being time whilst the mathematical model of Abramson and Kenkre is a system of partial differential equations (PDEs) with the dependent variable being r_s, r_i and the independent variable being time and spatial variable *x*. This will be done in chapter four.

In chapter five, we conduct a literature study related to population harvesting and extend the basic model of Abramson and Kenkre to include the process of harvesting. We study both theoretically and computationally the impact of different harvesting strategies on the spread of the hantavirus infection.

In chapter six, we discuss the role of biodiversity in hantavirus infection with our primary source of reference being a paper written by Peixoto and Abramson (2006). This paper assumes that the other species (aliens) which inhabit the ecosystem with rodents are competitors for resources but are not predators. We modify the Peixoto and Abramson (2006) biodiversity model to include the effect of

aliens as predators. We analyse the modified model and also study the predictions of the modified model.

Human infection model is used to study the effect of the human population on the spread of the hantavirus infection. Hantavirus is a serious disease to human because it is easily transmitted by exposure of bite and scratch from the infected rodent. Therefore, we extend the Li et al. (2011) human infection model to include the effect of human population. In chapter seven, we develop and analyse a hantavirus model which incorporates infection.

In chapter eight, we will utilize the reaction-diffusion systems in order to study the spatial effects such as movement of the rodents and alien (as predator) populations from one spatial location to another in a finite habitat. Therefore, we modify the Peixoto and Abramson (2006) biodiversity model to include the effect of aliens as predators and spatial effects of diffusion. The spatial effects mean that, it includes the effects of habitat geometry and heterogeneity of environment on the extinctions, persistence and coexistences of species. We focus our study on the effects of diffusion mechanism, particularly the diffusion constant D, on extinction and persistence phenomena of the modified model via analytical and numerical experiments.

Finally, in chapter nine, we present the conclusions of the research and discuss possible avenues for further work in hantavirus infection.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

The discussion of literature review in this thesis is focused on the issues we have listed in the objective and scope in section 1.2. In section 2.2 and 2.3, literature review related to first and second objectives considered in this thesis via; mathematical modeling of hantavirus infection and the effect of spatial extension in a Abramson and Kenkre model of hantavirus infection is discussed. The discussion of modeling population harvesting of rodents for the control of hantavirus infection is further extend to *AK* model in section 2.4. This is related to the third objective of this thesis. Then, in section 2.5, literature review about the effect of biodiversity on the spread of hantavirus infection is discussed. This is related to the fourth objective of this thesis. Then, literature review related to fifth and sixth objectives considered in this thesis via; modeling the transmission dynamics on the spread of the hantavirus infection and the effect of reaction-diffusion on a biodiversity model of hantavirus infection in section 2.6 and section 2.7, respectively.

2.2 MATHEMATICAL MODELING OF HANTAVIRUS INFECTION

Hantaviruses are viruses carried by certain kinds of rodents. The viruses can be killed by most household disinfectants. Hantaviruses represent significant pathogens and can cause hemorrhagic fever with renal syndrome (HFRS) or epidemic nephritis (EN) and hantavirus cardiopulmonary syndrome (HCPS). Both diseases are characterised by endothelial dysfunction. Endothelial dysfunction, in turn, is characterised by increased permeability caused either by direct endothelial infection or by indirect effects like the production of various cytokines by activated leukocytes (Kraus, 1973). The Hantaan Viruses, Puumula virus, Dobrava virus and Seoul are variations of hantaviruses that can cause HFRS. HPS is a medical disease caused by several hantaviruses in North and South America (www.cfsph.iastate.edu/ Factsheets/ pdfs/ hantavirus.pdf., accessed 12 September 2008).

Hantaviruses live within various species of rodents (i.e. rats and mice) without causing any symptoms and are transmitted to humans by direct or indirect contact with the urine, excreta or saliva from infected rodents (Yusof, 2008). The mortality rate associated with HFRS ranges from approximately 0.1 to 3% for Puumala virus infections, to more or less 5 to 15% for HFRS caused by Hantaan and Dobrava virus and around 1% with Seoul virus infections. The mortality rate for HPS caused by Sin Nombre and New York virus is estimated to be 40 to 50% (Christie and Guadagno, 2003).

There are three most common symptoms of HFRS mentioned in the name of the disease. Fever is one while the second symptom is malfunction of the kidneys. The final symptom is a low platelet count. Platelets are blood cells that promote the clotting of blood (Yusof, 2008).

Lerner and Lerner (2003) stated that HPS develops in four stages. The first stage is the incubation period where usually patients may exhibit no symptoms. The warning signs stage is when the patient begins with a fever, muscle aches, backache, and abdominal upset. Meanwhile the patient slips into the cardiopulmonary stage rapidly, sometimes within a day or two of initial symptoms; sometimes as long as 10 days later. There will be a drop in blood pressure, shock, and leaking of the blood vessels of the lungs, which results in fluid accumulation in the lungs, and subsequent shortness of breath. Finally, the convalescent stage: there is a rapid recovery, usually within a day or two. However, abnormal liver and lung functioning may persist for six months.

In this thesis, we have chosen to examine the mathematical model of hantavirus infection, in particular, the Abramson and Kenkre model because not many researchers discussed the phenomenon of the spread of hantavirus infection and its solution. Based on year 2000 data, the mortality rate associated with HFRS ranges from approximately 5 to 15% for Hantaan and the mortality rate for HPS caused by Sin Nombre virus is estimated to be more than 45% (Faulde et al., 2000). It has a high mortality disease and we would like to be one of the researchers who contribute to research about hantavirus. Another reason is because this fascinating

subject has a lot of aspects that are still unexplored. We feel fascinated by all these aspects may be one day the researches can help reduce or eliminate virus and the way disease is transmitted can be stopped.

The construction of the basic model of Abramson and Kenkre (*AK*) incorporates decay by death of the mice population, the increase by birth and effect of the environment to stabilize the population (Goh et al., 2009). This model is able to successfully explain several field observations as environmentally controlled phase transitions, thus providing an analytical support to biological hypotheses such as the trophic cascade (Abramson, 2007b).

Abramson and Kenkre formulated a simple mathematical model to analyse the spatio-temporal patterns in the spread of hantavirus. Results derived from their paper show environmental conditions strongly affect the dynamics and persistence of the infections.

The basic model of Abramson and Kenkre proposed a single rodent species without movement (i.e. no spatial extension and only temporal variable is present). Here the total population rodents are divided into two groups, one is susceptible and another is infected. The model is:

$$\left.\begin{aligned} \frac{dr_s}{dt} &= br - cr_s - \frac{r_s r}{k(t)} - ar_s r_i \\ \frac{dr_i}{dt} &= -cr_i - \frac{r_i r}{k(t)} + ar_s r_i \end{aligned}\right\} \quad \ldots \quad (2.1)$$

where r_s and r_i are the populations of susceptible and infected rodents, respectively,

where $r(t) = r_s(t) + r_i(t)$ is the total population of rodents. For abbreviation, we shall refer to this model (equation (2.1)) as the basic *AK* model.

Birth: *b* is birth rate of rodents, the multiplication of *b* and *r* represents the births of rodents, all of them born vulnerable to the infection at a rate proportional to the total population assuming that all rodents contribute equally to the reproduction process.

Deaths: *c* represents the natural death rate. The infection does not cause deaths among rodents.

Competition: $-\frac{r_s r}{k}$ or $-\frac{r_i r}{k}$ represents a limitation process in the rodent population growth due to competition for resources shared between r_s and r_i. In the basic model *k* depends on time and is a "environmental parameter". Higher values of *k* represent higher availability of water, food, shelter and other resources for the rodents that rodents can use to thrive. According to Campbell et al. (2008), *k* is the maximum number of rodents which can be accommodated within a defined space or habitat and environment that can support them over an indefinite period of time. It is determined by the availability of nutrients, water, shelter and breeding sites. If *k* is increased the number of the population tends to increase to take advantage.

Infection: $ar_s r_i$ represents the number of susceptible rodents that get infected due to an encounter with an infected rodent (e.g. bites from fights) at a rate *a* (assumed constant). The value *a* is known as the "aggression parameter". The infection is chronic, infected rodents do not die of it, infected rodents do not lose their

infectiousness for their whole life. For these reasons, this single term was deemed by *AK* to adequately describe the infection dynamics of the two subpopulation.

According to *AK*, there is a critical value of environmental parameter $\left(k_c = \frac{b}{a(b-c)}\right)$ that separates two distinctive regimes. If the environmental parameter k is smaller than k_c, r_i tends to zero and the infection dies away. If $k > k_c$, the infection thrives since there is an increase in edible resources. As the environmental parameter will vary with time, the system will undergo transitions from one state to another. This corresponds to the observed sporadic appearance and disappearance of the infection mentioned in the introduction.

Abramson and Kenkre extended the basic *AK* by taking into account the rodent movement by diffusion (Goh et al., 2009). This model is called the spatial extension of the *AK*. Results from the movement of the rodents population over the terrain and diversity of the landscape, resulting in the uniform distribution of the rodents occurring in an ecosystem. In consequence, the diffusion can affect a variety of different quantities.

The basic model can be spatially extended to take into account of the movement of rodents in one-dimension by including a diffusive term. The dimension of a space is informally defined as the minimum number of coordinates needed to specify any point within it. This model is one-dimension partial differential equation (PDE) because it has one spatial derivative in *x*. Equation (2.2) is the spatial

extension of the *AK* model. The extended Abramson and Kenkre model is of the form :

$$\left.\begin{aligned}\frac{\partial r_s}{\partial t} &= br - cr_s - \frac{r_s r}{k(x,t)} - ar_s r_i + D_s \nabla^2 r_s \\ \frac{\partial r_i}{\partial t} &= -cr_i - \frac{r_i r}{k(x,t)} + ar_s r_i + D_i \nabla^2 r_i\end{aligned}\right\} \quad \ldots (2.2)$$

where $\nabla^2 r_s$ and $\nabla^2 r_i$ are the second partial derivatives of the populations of susceptible and infected rodents respectively where r_s and r_i are now function of x and t. D is diffusion constant and is expected to be different for susceptible and infected rodents. The analysis by Abramson and Kenkre (2002) for small and moderate values of the diffusion constant shows that the infected population survives in the regions of high environmental parameter and becoming extinct in the rest. These "islands" of infection become reservoirs or refugia of the virus and it is from these locations that the disease will spread when environmental conditions become favourable.

Abramson and Kenkre (2002) did not describe the spread of hantavirus via numerical experiments but only presented the characteristics of the basic model. In chapter 3, we analyse the effects of hantavirus infection through illustrations and highlight some of the characteristics of the basic *AK* (i.e. equation (2.1)) model using numerical experiments.

2.3 EFFECTS OF SPATIAL EXTENSION IN THE ABRAMSON AND KENKRE MODEL OF HANTAVIRUS INFECTION

Recall that model (2.2) which is the spatial extension of the *AK* (2002) with diffusive term of single rodent species. The model is of the form

$$\left.\begin{aligned}\frac{\partial r_s}{\partial t} &= br - cr_s - \frac{r_s r}{k(x,t)} - ar_s r_i + D_s \nabla^2 r_s \\ \frac{\partial r_i}{\partial t} &= -cr_i - \frac{r_i r}{k(x,t)} + ar_s r_i + D_i \nabla^2 r_i\end{aligned}\right\} \quad \ldots (2.2)$$

where r_s and r_i are the populations of susceptible and infected rodents, respectively, where $r(t) = r_s(t) + r_i(t)$ is the total population of rodents. The value *a* is the transmission rate responsible for infection, *b* is the birth rate, *c* is the natural death rate and the resources (food, water, vegetation) are described by *k* which is generally time and space dependent. *k* is also can be called as environmental parameter. According to Kumar et al. (2010), ∇^2 is the one-dimensional Laplacian i.e. $\frac{\partial^2}{\partial x^2}$. Yates et al. (2002) stated that Abramson and Kenkre model are associated with characteristic features of any population that plays the role of the reservoir of an infectious disease. The unit for diffusion constant, *D*, is metre^2 per day. *D* is a diffusion constant with which susceptible and infected rodents moves over the terrain. According to Abramson et al. (2001), diffusion is defined as typically a limit of a more coherent motion interrupted by scattering events which is valid when the scattering events are extremely frequent.

Using numerical methods, Abramson and Kenkre (2002) considered first a one-dimensional spatial landscape, consisting of a spot of high environmental parameter $(k > k_c)$ in the center of a larger region of low environmental parameter $(k < k_c)$. A steady state is attained in which the infected population is focused at the spot of higher *k* in an arbitrary initial condition of the population. This spot constitutes a "refugium". For a two-dimensional landscape, the susceptible rodent population occupies the entire landscape, with a nonhomogeneous density. The infected population survives in a patchy pattern when the values of the diffusion coefficient is small and moderate, only in the regions of high environmental parameter *k*, becoming extinct in the rest. These "islands" of infection become reservoirs of the virus or "refugia", which are the places of highest risk for human exposure and contagion. Abramson and Kenkre (2002) noted that this is precisely what was observed in the field.

Kumar et al. (2009) and Kumar et al. (2010) have conducted research on the Abramson and Kenkre model (which incorporates spatial extension). Kumar et al. (2009) studied the Allee phenomenon which causes an imperfect pitchfork bifurcation instead of the transcritical bifurcation in the spread of an infectious disease. They state that the bifurcation is imperfect as the system under study is not symmetric under reflection. A most relevant result involved the environmental spatial inhomogeneities (modulations) which provides a linkage between the landscape structure of species' resource habitats and the matrix surrounding it (Kumar et al., 2009). The bifurcation they discovered was more evident when calculating the mean value of the population densities. They showed the existence of a critical value of the spatial modulation wave number where the behaviour of the

systems completely changes, displaying bistable behaviour that depends on the initial conditions. Kumar et al.'s (2010) study of infection of hantavirus is classified by spatially dependent environmental issues. The purpose of their research was to provide the mathematical basis for understanding constraints and behaviours of rodents with hantavirus interaction through time.

By referring to Abramson and Kenkre model, Kumar et al. (2010) states that the infection population r_i decreases with a decrease in a region of length L and vanishes completely at the critical value of the region of length L_c which means critical length. Kumar and Kenkre (2011) stated that the critical length of the favorable segment corresponds to the situation that the random walker traverses the length of the segment diffusively in the time necessary for growth, and falls prey to the harsh conditions outside the segment. Meanwhile the susceptible population r_s, does not vanish even for the value of region of length equal to zero $(L = 0)$. Only the infection population r_i exhibits a transition. The transition means that, if it were desirable to achieve the disappearance of refugia in a given landscape, it would not be necessary to drop the environment resources below the critical value expected in the absence of rodent diffusion.

Note that in the absence of diffusion $\left(D_s \nabla^2 r_s = D_i \nabla^2 r_i = 0\right)$, we will get the basic model of Abramson and Kenkre (2002):

$$\frac{dr_s}{dt} = br - cr_s - \frac{r_s r}{k} - ar_s r_i$$

$$\frac{dr_i}{dt} = -cr_i - \frac{r_i r}{k} + ar_s r_i$$

The papers of Abramson and Kenkre (2002) and Kumar et al. (2010) were rather theoretical in nature and not much numerical evidence was presented. Hence, this study will explore and validate the use of more substantial numerical evidence in detail in Chapter 4.

2.4 MODELING POPULATION HARVESTING OF RODENTS FOR THE CONTROL OF HANTAVIRUS INFECTION

There have been recent works on population harvesting by Bairagi et al. (2009) and Matsuoka and Seno (2008). According to Bairagi et al. (2009), epidemiology can encroach into ecology and change the system dynamics significantly. In population ecology, predator-prey interaction in presence of parasites can produce more complex dynamics including switching of stability, extinction and oscillations. Bairagi et al. (2009) states that harvesting can play a crucial role in a host-parasite system and reasonable harvesting can remove a parasite from their host. In their paper, the role of harvesting in a predator-prey-parasite system has been studied. Their study shows that impulsive harvesting can control the cyclic behavior of the system populations leading to the persistence of all species and obtain disease-free stable equilibrium.

Matsuoka and Seno (2008) analyzed a time-discrete mathematical model of host-parasite population dynamics with harvesting, in which the host can be regarded as a pest. A portion of the host population is harvested at a moment in each parasitism season with the principal target being the host. However, the parasite population may also be affected and reduced by a portion. They investigate the

condition under which the harvesting of the host results in an eventual increase of its equilibrium population size.

Xia et al. (2009) have researched the effects of harvesting and time delay on two different types of predator-prey systems with delayed predator specific growth and Holling type II functional response. The predator-prey model is harvested at a constant rate given by

$$\frac{dr}{dt} = \alpha\left(1-\frac{r}{k}\right)r - \frac{mrz}{\delta(A+r)} - h_r$$
$$\frac{dz}{dt} = z\left(-D+\frac{mr}{A+r}\right) - h_z$$

where r and z are the densities of the prey and predator population at the time t, respectively. The value α is the intrinsic growth rate of the prey, k is the carrying capacity of the prey; m is the maximum growth rate of predators; δ is the yield conversion factor for predators feedings on the prey, A is the half saturation constant for the predators which is the prey density at which the functional response is half maximal, D is the death rate of predators, h_r and h_s are constant harvesting rates for the prey and predators, respectively.

Shi (2006) has developed a simple mathematical model associated with the seasonal or periodic harvesting model in time variable t. Shi (2006) added a simple periodic harvesting term $h(1+\sin(wt))$ to the logistic equation, where $h>0$ is a parameter measuring the harvesting rate. For fixed time t, Shi (2006) assumed the harvesting is proportional to the size of the population. The periodic function $(1+\sin(wt))$ is non-negative with period 2π; when $t=\frac{1}{w}\left(2m-\frac{1}{2}\right)\pi$, the harvesting